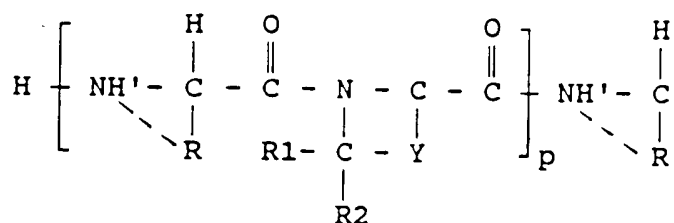


08/950,542

INHIBITORS OF DIPEPTIDYL-AMINOPEPTIDASE TYPE IV

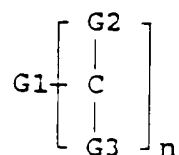
Abstract of the Disclosure

An inhibitory compound having the structure: Group I - Group II. Group I has the structure:

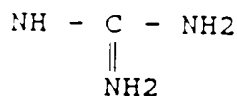


where H represents a hydrogen; C represents a carbon; O represents an oxygen; N represents a nitrogen; each R, independently, is chosen from the group consisting of the R groups of an amino acid, including proline; each broken line, independently, represents a bond to an H or a bond to one R group, and each H' represents that bond or a hydrogen; and p is an integer between 0 and 4 inclusive.

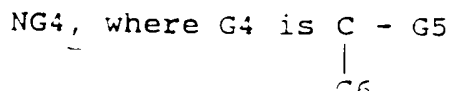
Alternatively Group I has the structure:



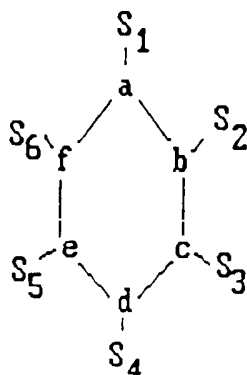
where n is between 0 and 3 inclusive, each G2 and G3 independently is H or C1 - 3 (one to three carbon atoms) alkyl, G1 is NH3 (H3 represents three hydrogens),



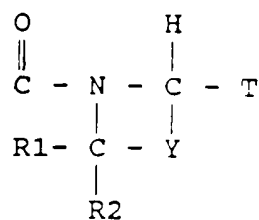
(H2 represents two hydrogens), or



where G5 and G6 can be NH, H, or C1 - 3 alkyl or alkenyl with one or more carbons substituted with a nitrogen. G1 bears a charge, and G1 and Group II do not form a covalently bonded ring structure at pH 7.0. Group I may also have the structure:



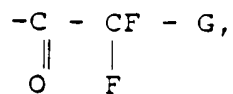
where one or two of the a, b, c, d, e, and f group is N, and the rest are C, and each S1 - S6 independently is H or C1 - C3 alkyl. Group I may also include a five membered unsaturated ring having two nitrogen atoms. Group II has the structure:



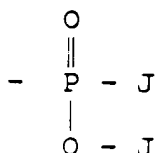
where T is a group of the formula:

$$\begin{array}{c}
 \text{D2} \\
 | \\
 - \text{B} - \text{D1}
 \end{array}$$

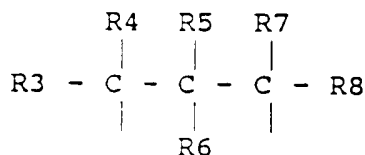
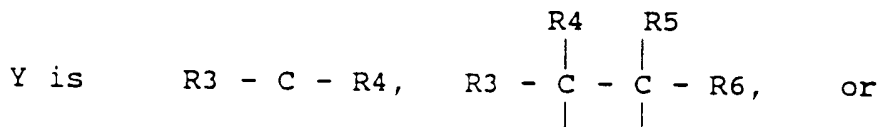
where each D1 and D2, independently, is a hydroxyl group or a group which is capable of being hydrolysed to a hydroxyl group in aqueous solution at physiological pH; a group of the formula:



where G is either H, fluorine (F) or an alkyl group containing 1 to 20 carbon atoms and optional heteroatoms which can be N, S (sulfur), or O; or a phosphonate group of the formula:

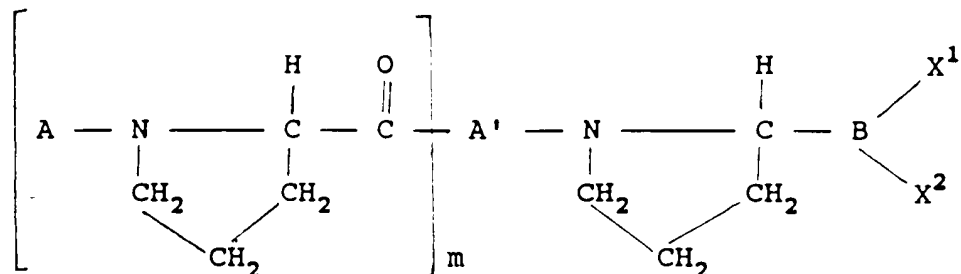


where each J, independently, is O-alkyl, N-alkyl, or alkyl. Each O-alkyl, N-alkyl or alkyl includes 1 - 20 carbon atoms and, optionally, heteroatoms which can be N, S, or O. T is generally able to form a complex with the catalytic site of a DP IV.



and each R1, R2, R3, R4, R5, R6, R7, and R8, separately is a group which does not significantly interfere with site specific recognition of the inhibitory compound by DP IV, and allows a complex to be formed with DP IV.

In another aspect, the invention features an inhibitor of DP-IV, having the structure:



wherein m is an integer between 0 and 10, inclusive; A and A' are L-amino acid residues such that the A in each repeating bracketed unit can be a different amino acid residue; the C bonded to B is in the L-configuration; the bonds between A and N, A and C, and between A and N are peptide bonds; and each X^1 and X^2 is, independently, a hydroxyl group or a group capable of being hydrolysed to a hydroxyl group at physiological pH.